

A dual diffusion model enables 3D molecule generation and lead optimization based on target pockets

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Abstract

Structure-based generative chemistry is essential in computer-aided drug discovery by exploring a vast chemical space to design ligands with high binding affinity for targets. However, traditional *in silico* methods are limited by computational inefficiency, while machine learning approaches face bottlenecks due to auto-regressive sampling. To address these concerns, we have developed a conditional deep generative model, PMDM, for 3D molecule generation fitting specified targets. PMDM consists of a conditional equivariant diffusion model with both local and global molecular dynamics, enabling PMDM to consider the conditioned protein information to generate molecules efficiently. The comprehensive experiments indicate that PMDM outperforms baseline models across multiple evaluation metrics. To evaluate the applications of PMDM under real drug design scenarios, we conduct lead compound optimization for SARS-CoV-2 main protease (Mpro) and Cyclin-dependent Kinase 2 (CDK2), respectively. The selected lead optimization molecules are synthesized and evaluated for their *in-vitro* activities against CDK2, displaying improved CDK2 activity. Structure-based generative chemistry is crucial in computer-aided drug discovery. Here, authors propose PMDM, a conditional generative model for 3D molecule generation tailored to specific targets. Extensive experiments demonstrate that PMDM can effectively generate rational bioactive molecules